CLINICAL EVIDENCE

# Genital herpes

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**QUESTIONS: What are the effects of antiviral treatment on a first episode of genital herpes? Which interventions reduce the impact of recurrent genital herpes? Which interventions prevent transmission of herpes simplex virus?**

## INTERVENTIONS

### Beneficial

Oral antiviral treatment during the first episode
Oral antiviral treatment taken at the start of a recurrence
Daily oral antiviral treatment in people with high rates of recurrence

### Key Clinical Points

- Evidence from randomized controlled trials (RCTs) shows that oral antiviral treatment reduces the duration of symptoms, lesions, and viral shedding in first and recurrent episodes of genital herpes and that daily treatment reduces the rate of recurrence
- Evidence from RCTs shows no significant difference in effectiveness or adverse effects between acyclovir (aciclovir), valaciclovir, and famciclovir
- Interventions to prevent sexual transmission have not yet been adequately assessed in RCTs
- The highest risk of mother-to-baby transmission is among women who are newly infected with genital herpes in late pregnancy. Interventions aimed at preventing infection in late pregnancy (such as serological screening and counseling) have not been evaluated.
- The effect of cesarean section on mother-to-baby transmission has not been evaluated. The procedure carries the risk of excess maternal morbidity and mortality
- Limited evidence from RCTs suggests that antiviral treatment may reduce the number of pregnant women with genital lesions at term. Since women with genital lesions at term are usually offered cesarean sections, antiviral treatment may reduce the rate of cesarean sections

### Likely to be beneficial

Daily oral antiviral treatment in late pregnancy in women with a history of genital herpes

### Unknown effectiveness

Psychotherapy
Interventions to prevent sexual transmission
Cesarean section in women with genital lesions at term
Serological screening and counseling in late pregnancy

### Definition

Genital herpes is the result of an infection with herpes simplex virus type 1 or 2 (HSV-1 or HSV-2), which causes ulceration in the genital area. HSV infections can be classified on the basis of virological and serological findings. Types of infection include: first-episode primary infections (HSV in a person without evidence of previous infection—that is, no antibodies to HSV-1 or HSV-2); first-episode non-primary infections (HSV-2 in a person who previously had antibodies to HSV-1); and first recognized recurrence of HSV-2 or HSV-1 in a person who previously had antibodies to HSV-2 or HSV-1. Recurrent genital herpes is caused by reactivation of latent HSV.

### Prevalence

Genital herpes infections are among the most common sexually transmitted diseases. Seroprevalence studies show that 22% of adults in the United States have HSV-2 infection[1]; a U.K. study showed that 23% of adults attending sexual medicine clinics and 7.6% of blood donors in London had antibodies to HSV-2.[2]

### Etiology

Both HSV-1 and HSV-2 can cause a first episode of genital infection, but HSV-2 is more likely to cause recurrent disease.[3] Most people with HSV-2 infections are not aware that they have genital herpes, as their symptoms are mild. However, these people serve as a source of new infections for sexual partners and newborns.[4,5]

### Prognosis

The sequelae of HSV infection include neonatal HSV, opportunistic infections in immunocompromised people,

recurrent genital ulceration, and psychosocial morbidity. HSV-2 infection is associated with an increased risk of HIV transmission and acquisition. The commonest neurological complications are aseptic meningitis (reported in about a quarter of women during primary infection) and urinary retention. The risk of neonatal infection is high (41%, 95% CI 26% to 56%) in babies born to women who acquire infection near the time of labor[6,7] and low (<3%) in women with established infection, even in those who have a recurrence at term. About 15% of neonatal infections result from postnatal transmission from oral lesions.

### Aims

To reduce the morbidity of the first episode, to reduce the risk of recurrent disease after a first episode, and to prevent further transmission.

### Outcomes

Severity and duration of symptoms, healing time, duration of viral shedding, rates of recurrence, psychosocial morbidity, rates of transmission, adverse effects of treatment

### Methods

Medline was searched for articles published from 1992 to 1998 using the terms herpes simplex virus, valaciclovir, famciclovir, cidofovir, trifluridine, and neonatal herpes. Preliminary results of clinical trials published in the abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy and the International Society for STD Research were also included. Experts in the field, as well as makers of antiviral drugs, were contacted to identify completed studies which were undergoing peer review but had not yet been published.

## QUESTION: What are the effects of antiviral treatment on a first episode of genital herpes?

Evidence from RCTs shows that oral antiviral treatment decreases the duration of lesions, symptoms, and viral shedding and prevents neurological complications in patients with first-episode genital herpes. It is more convenient than intravenous treatment and more effective than topical treatment. Limited data provide no evidence that oral antiviral treatment reduces the rate of recurrence compared with placebo. Evidence from RCTs shows no significant difference between acyclovir (aciclovir), valaciclovir, and famciclovir.

### Benefits

No systematic review

### Immediate effects

We found several RCTs (>350 men and women) of oral acyclovir (aciclovir) for the treatment of first-episode genital herpes. Compared with placebo, acyclovir 200 mg 5 times a day decreased the duration of viral shedding (2 vs 10 days), pain (5 vs 7 days), and time to healing of lesions (8 vs 14 days) and prevented formation of new lesions. Neurological complications (aseptic meningitis and urinary retention) were also reduced. Numbers were small, so no firm estimates of effectiveness were available.[8-12]

### Different regimens

In an international trial of 643 healthy adults with first-episode genital herpes, valaciclovir 1000 mg twice daily was compared with acyclovir 200 mg 5 times a day for 10 days.[13] No significant differences were noted between the 2 drugs in any clinical or virological variables. Another RCT evaluated 3 different doses of famciclovir (125 mg, 250 mg, or 500 mg 3 times a day) versus acyclovir 200 mg 5 times a day in 951 adults with first-episode genital herpes.[14] No significant differences were found.

### Recurrence rates

A meta-analysis of 2 placebo-controlled RCTs in 61 participants showed no significant difference in time to recurrence or frequency of recurrence between those given acyclovir and those given placebo.[15]

### Harms

Adverse effects (mostly headache and nausea) were rare and occurred with similar frequency on acyclovir (aciclovir), valaciclovir, famciclovir, and placebo.

### Comment

Intravenous and topical acyclovir have also been studied. Oral acyclovir is more convenient than intravenous and more effective than topical preparations.[16]

## QUESTION: Which interventions reduce the impact of recurrent genital herpes?

### OPTION: ANTIVIRAL TREATMENT AT THE START OF RECURRENCE

Evidence from RCTs shows that oral antiviral treatment taken at the start of recurrence reduces the duration of lesions, symptoms, and viral shedding in patients with recurrent genital herpes.

### Benefits

No systematic review. Several RCTs in >650 healthy adults with recurrent genital herpes were identified in a nonsystematic review published in 1990.[17] These evaluated 5 days of oral acyclovir 200 mg 5 times a day or 800 mg twice a

day initiated at the first sign of recurrence. Compared with placebo, treatment decreased viral shedding (1 vs 2 days) and duration of lesions (5 vs 6 days). An RCT in 739 people with recurrent genital herpes compared patient-initiated valaciclovir 500 mg or 1000 mg twice daily for 5 days with placebo. Valaciclovir decreased the duration of episodes (4 vs 6 days), reduced viral shedding (2 vs 4 days), and increased the rate of aborted recurrences (31% vs 21%).[18] An RCT of famciclovir (125 to 500 mg twice daily) versus placebo in 467 people with recurrent genital herpes found a significant reduction in the duration of lesions (5 vs 4 days) and viral shedding (3 vs 2 days).[19] Differences were significant for all doses of famciclovir ($P<0.01$). Two RCTs in 1939 patients found no significant difference between valaciclovir and acyclovir.[20, 21]

### Harms

Adverse effects (mostly headache and nausea) were rare and occurred with similar frequency during treatment with acyclovir, valaciclovir, famciclovir, and placebo.

### Comment

The benefit was greater if the patient initiated treatment at the first symptom or sign of recurrence.[22] People with recurrent herpes can learn to recognize recurrences early and should have an adequate supply of medicine at home.

## OPTION: DAILY MAINTENANCE ANTIVIRAL TREATMENT

Evidence from RCTs shows that daily maintenance treatment with oral antiviral agents reduces the frequency of recurrences and viral shedding in patients with genital herpes. Daily treatment may also improve psychosocial function.

### Benefits

No systematic review

### Recurrence rates

Several RCTs were identified in a nonsystematic review published in 1990.[17] These compared daily treatment with varying doses of acyclovir versus placebo for prevention of recurrences in people with genital herpes. Most participants had a history of frequent recurrences (6 or more each year). Daily acyclovir reduced the recurrence rate by 74% to 93%, and recurrences were shorter than those that occurred without treatment (3.5 vs 5 days).[17] Of 210 adults who completed 5 years of continuous treatment with acyclovir 400 mg twice daily, 53% to 70% were free of recurrence each year.[23]

The first year of this study was a double-blind, placebo-controlled RCT in 1146 adults. Those on acyclovir had significantly fewer recurrences during the first year (1.7 vs 12.5, $P<0.0001$). Two RCTs evaluated daily valaciclovir.[24, 25] In a 1 year study of 479 adults, 40% to 50% of people who received valaciclovir 500 mg or 1000 mg once daily, valaciclovir 250 mg twice daily, or acyclovir 400 mg twice daily were free from recurrence, compared with 5% of people who received placebo.

Two RCTs evaluated daily famciclovir for up to 1 year in adults with frequently recurring genital herpes.[26, 27] In a 1-year study of 455 adults treated with varying doses of famciclovir, the median time to first recurrence was 11 months for famciclovir 250 mg twice daily and 1.5 months for placebo.

### Viral shedding

One RCT has evaluated the effect of daily maintenance treatment on viral shedding in women with recently acquired genital HSV-2 infection. Participants provided swabs for viral cultures daily for 70 days while receiving acyclovir 400 mg twice daily or placebo.[28] Viral shedding was reduced by 95% on days with reported lesions and by 94% on days without lesions.

### Psychosocial morbidity

There were no RCTs that assessed this outcome. The effect of daily acyclovir on psychosocial morbidity has been assessed in a prospective observational study of 102 men and women with frequently recurring genital herpes.[29] Patients were questioned to assess their mental health and psychosocial functioning. Levels of anxiety and depression fell from 63% to 26% in 80% of patients who completed 3 months of acyclovir treatment.

### Harms

Daily treatment with acyclovir, famciclovir, and valaciclovir was well tolerated. Patients on acyclovir have been followed for up to 7 years and on famciclovir and valaciclovir for up to 1 year. Nausea and headache were infrequent, and patients rarely discontinued treatment because of adverse effects. Whether daily maintenance treatment increases high-risk sexual behavior has not been studied. There is no evidence that daily treatment with acyclovir results in the emergence of acyclovir-resistant HSV during or after cessation of treatment in healthy adults.[30]

### Comment

Although continuous treatment is safe, discussion of cessation of treatment is reasonable on an annual basis, as some patients experience less frequent recurrences with time or experience less distress during the recurrences. Several effective dosages have been studied: most patients prefer regimens of once- or twice-daily doses. Patients with frequent recurrences may benefit from twice-daily treatment.

### OPTION: PSYCHOTHERAPY

The effects of psychotherapy on the rate of recurrence of genital herpes have not yet been adequately studied.

#### Benefits

A systematic review published in 1993 identified 6 studies of psychotherapeutic interventions in 69 participants (4 studies had <10 participants).[31] Interventions varied from hypnotherapy and progressive muscle relaxation to cognitive therapy and multidimensional psychosocial intervention. In the largest study, 31 patients with 4 or more recurrences each year were randomly allocated to treatment with psychosocial intervention, social support, or a place on a waiting list. Participants receiving psychosocial intervention had significantly lower recurrence rates (6 per year) compared with the pretreatment frequency (11 per year) and with the other groups (11 per year).

#### Harms

No adverse effects were noted.

#### Comment

Small numbers of patients, inadequate controls, and subjective and retrospective assessment of recurrence frequency at baseline limit the usefulness of these studies. Controlled studies that include prospective clinical evaluation of disease activity are needed.

## QUESTION: Which interventions prevent transmission of HSV?

### OPTION: CONDOMS, ANTIVIRAL TREATMENT, IMMUNIZATION

The effectiveness of these interventions in preventing HSV transmission has not been adequately studied.

#### Condoms

No RCTs. In a prospective cohort study of 144 couples in the United States discordant for HSV-2 infection, use of condoms or diaphragms was associated with a lower rate of HSV-2 acquisition, 5.7% versus 13.6% (P=0.2).[32]

#### Antiviral treatment

No RCTs have looked at rates of transmission. RCTs have shown, however, that daily antiviral treatment decreases the frequency of clinical and subclinical viral shedding (see above). There is no direct evidence that treatment reduces HSV transmission in serologically discordant couples.

#### Immunization

No effective vaccines are currently available.

#### Harms

The same as for individual interventions

#### Comment

Controlled studies of condoms for the prevention of HSV-2 transmission are unlikely to be done. As HSV reactivates over a wide genital area, condoms may offer less protection against genital herpes than for STDs characterized by urethral or cervical discharge.

### OPTION: CESAREAN SECTION

The effect of Cesarean section on the risk of neonatal herpes is uncertain. The procedure carries the risk of excess maternal morbidity and mortality.

#### Benefits

No RCTs have assessed the benefits of Cesarean section. In the Netherlands, women with recurrent genital herpes at delivery have been allowed vaginal birth since 1987. This policy has not resulted in an increase of neonatal herpes: 26 cases occurred from 1981 to 1986 and 19 cases from 1987 to 1991.[7]

#### Harms

Cesarean sections are associated with significant maternal morbidity and mortality. The number of maternal deaths caused to prevent 1 neonatal death from HSV has been estimated as 0.57.[33] The estimated cost of the excess of cesarean sections is $2.5m per case of neonatal HSV averted.

#### Comment

Countries vary in their approach to the obstetric management of women with recurrent genital herpes at delivery. Women with genital lesions at term have Cesarean sections in the United States and in the United Kingdom, with attendant maternal and financial costs. The risk of neonatal infection is high (41%, 95% CI 26% to 56%) in babies born to women who acquire their infection near the time of labor[6,7] and low (<3%) in women with established infection, even in those who have a recurrence at term. Most women who acquire infection toward the end of pregnancy are undiagnosed, and most cases of neonatal HSV infection are acquired from women without a history of genital herpes. The available evidence suggests that prevention of neonatal HSV should focus on preventing infection in late pregnancy.

### OPTION: ANTIVIRAL TREATMENT DURING PREGNANCY

There is limited evidence from a systematic review of RCTs that acyclovir reduces the rate of cesarean section in women with first or recurrent episodes of genital HSV

during pregnancy. The risk of rare adverse events has not been adequately studied.

### Benefits

A systematic review published in 1998 identified 3 studies, including 2 RCTs, of daily acyclovir versus placebo in 210 near-term pregnant women with genital herpes.[7] The dose and duration of acyclovir and the populations enrolled differed in each study. Cesarean section was performed in women with genital lesions at labor. All 3 studies found lower rates of Cesarean section in women treated with acyclovir: 8% versus 34% (P=0.02), 13% versus 33% (P=0.03) and 13% versus 25% (P=0.2).

### Harms

No adverse effects for women or newborns were reported.

### Comment

The number of women was small, and rare events, such as an increase in asymptomatic viral shedding or acyclovir-related obstructive uropathy in the newborns, would be difficult to detect.

## OPTION: SEROLOGICAL SCREENING AND COUNSELING DURING PREGNANCY

Neither serological screening with type-specific assays to identify women at risk for HSV acquisition in late pregnancy nor counseling to avoid genital-genital and oral-genital contact in late pregnancy has been evaluated.

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